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Normal Hemoglobin A1c Variability in Early Adolescence: Adult Criteria for Prediabetes Should be Applied with Caution

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Abstract

American Diabetes Association adult criteria are used to screen youth for diabetes, but little is known about normal glycemia in youth. In the HEALTHY Study (total n=8814), hemoglobin A1c (HbA1c) was 5.7% in 2% of normal weight youth. This suggests need for cautious interpretation of prediabetes HbA1cs in youth.

The meaning of measures of glucose in youth are not fully understood, as all youth experience metabolic changes during puberty, including transient insulin resistance, and little is known about the impact of these metabolic changes on the distribution of glycemia. However, despite this lack of knowledge, the American Diabetes Association (ADA) adult criteria for the diagnosis of diabetes and prediabetes have been extrapolated to youth. In 2010 the ADA added criteria for use of the hemoglobin A1c (HbA1c) for screening and diagnosis of diabetes and prediabetes.¹ The HbA1c has some advantages over the traditional diagnostic tests (fasting or 2-hour glucose on the oral glucose tolerance test (OGTT)), including lack of a need for fasting, lack of need for timed samples, and less influence of acute circumstances of the testing day. The decision to add HbA1c was based on improvements in assay standardization, correlation with 2-hour glucose, and population studies demonstrating increased prevalence of retinopathy in adults at high risk for type 2 diabetes.^{2, 3} In adults, a prediabetes HbA1c has been shown to predict progression to diabetes, as well as risk for retinopathy.³ However, studies validating the use of a prediabetes HbA1c to predict risk for progression to diabetes or diabetes complications in youth are lacking. We and others have shown correlation of HbA1c with other measures of glycemia, eg, oral glucose tolerance testing and continuous glucose monitoring, in the context of

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screening for type 2 diabetes in obese youth.^{4, 5} However, in the absence of a full understanding of physiologic changes in glycemia during puberty, the meaning of any of these measures of glycemia remains unclear. Finally, little is known about the impact of race/ethnicity on the HbA1c distribution in youth without diabetes.

The HEALTHY Study included a large cohort of normal weight and overweight/obese ethnically and racially diverse 6th and 8th grade students in 7 urban field sites. This secondary analysis of data from the HEALTHY cohort will focus on the distribution of HbA1c in normal weight participants and the impact of race/ethnicity on this distribution and the difference in distribution of HbA1c in normal weight youth compared with youth who are overweight/obese.

Methods

The HEALTHY study was a randomized, cluster-design study designed to test the impact of a school-based intervention on diabetes risk factors in youth deemed at-risk for dysglycemia because of race/ethnicity and socioeconomic status. Primary outcomes and detailed methods have been extensively published.^{6, 7} Briefly, students in 42 schools (21 intervention, 21 control), selected for >50% of students eligible for free or reduced lunch and/or >50% non-Hispanic black or Hispanic students, were assessed at 6th and 8th grade. Youth were excluded if they had known diabetes or a condition that precluded them from participation in physical activity. Normal weight was defined as a BMI <85th percentile for age and sex. For the assessments, students were told to fast after midnight. Anthropometrics and venipuncture were performed in a school setting. Puberty stage was determined by self-assessment of Tanner stage.⁸ All laboratory measures were performed at the University of Washington Northwest Lipid Research Laboratory (Seattle, WA). HbA1c was measured by high-performance liquid chromatography (HPLC, G-7 Tosoh Biosciences Inc). The laboratory equipment was certified under the National Glycohemoglobin Standardization Program Level 1 against the Diabetes Control and Complications Trial Reference Method. The intra- and inter-assay coefficients of variation are 0.047% and 0.070%, respectively. The study was approved by the institutional review board at each university.

In total 12,671 assessments were conducted as a part of HEALTHY in either 6th or 8th grade, some only once but others on both occasions. This analysis included a subset of these assessments with the following exclusions: For those assessed on both occasions, we excluded 162 who regressed in their pubertal assessment. We excluded any 8th grade assessments (N=3,079) at a middle school randomized to receive the integrated intervention. Additionally, we excluded 165 who were either younger than 11 or older than 15 (due to small sample size) and 289 who did not have a measured HbA1c. A total of 2,022 participants contributed data at both 6th and 8th grade. The sample was then divided into normal weight (BMI < 85th percentile for age and sex, N=4,603) and overweight/obese (N=4,211). Descriptive statistics, including means, SDs, and percentages were calculated for all variables. Differences in HbA1c values by weight class were assessed using a generalized linear mixed model with a nested random effect to account sources of variability within and between schools. All *P* values reported within this paper represent testing of secondary outcomes from a large cluster randomized controlled trial and the hypotheses being tested

were not pre-specified in the trial design. Thus, the study was not specifically powered to perform the analyses in this manuscript. SAS 9.4 statistical software (SAS Institute, Cary, NC, USA) was used for analysis.

Results

A total of 8,814 youth (n=4,603 normal weight and n=4,211 youth with obesity) were included in these analyses. The primary analysis was comprised of normal weight girls (n=2,526) and boys (n=2,077) aged 11–15 years; The Table shows demographics by grade. Figure, A represents the distribution of HbA1c in the normal weight cohort. A total of 99 (2.2%) of these healthy youth had an HbA1c in the prediabetes range (5.7% and <6.5%)², as high as 6.2%. Distribution of HbA1c was similar between the self-reported puberty stages (data not shown). Distribution of HbA1c was also similar for the 2.8% of participants who were underweight at the time of assessment (n=130, median HbA1c 5.2%, range 3.9–6.1%).

Figure, C–E depicts the distribution of HbA1c by race/ethnicity and demonstrates an HbA1c distribution for Non-Hispanic black youth that is significantly skewed to the right when compared with Non-Hispanic white and Hispanic youth. Notably, 7.1% of normal weight black youth have an HbA1c 5.7%, and only 1.3% of Hispanic and 0.1% of white youth have an HbA1c in the prediabetes range².

Although the mean HbA1c was higher ($p<.0001$) in youth with overweight or obesity ($5.17 \pm 0.31\%$) compared with normal weight youth ($5.11 \pm 0.29\%$), the overall distribution of HbA1c was similar between the 2 cohorts (Figure, B).

Discussion:

In this large cohort of racially and ethnically diverse, mid-pubertal youth, 2 out of every 100 normal weight youth had an HbA1c in the “prediabetes” range. These elevated HbA1cs are highly unlikely to represent evolving diabetes, based on previously published epidemiologic data showing a much lower prevalence of diabetes in youth and diabetes characteristics different from this group of normal weight youth.^{9, 10} In adults, HbA1c in the prediabetes range has been shown to correlate with impaired glucose tolerance and impaired fasting glucose (IFG) by OGTT.¹¹ No similar study has been performed to date in youth. The OGTT is often considered the gold-standard for diagnosing diabetes; however, although there is evidence that adults with a 2-hour glucose in the prediabetes range are at high risk for progression to diabetes,³ the evidence for this association in youth is lacking. In a study of 117 obese adolescents, 45.5% of the 33 youth with impaired glucose tolerance (IGT) reverted to normal glucose tolerance after a mean of 20.4 months of follow-up,¹² though another large proportion (24.2%) did develop diabetes. The substantial variability in the OGTT seen over time may be, in part, related to variability in the physiologic changes in glucose metabolism occurring during the well-described transient insulin resistance of puberty.^{13, 14} This transient insulin resistance of puberty may also alter glucose metabolism in normal weight youth and lead to transient increases in glycemia, similar to changes seen with lipids during puberty.^{15–17} Therefore, there is not a full understanding of whether elevations into the adult prediabetes range of any measure of glycemia are meaningful in

youth. We did not find any differences in HbA1c by puberty stage in the HEALTHY cohort. However, because of the large sample size and epidemiologic nature of the parent study, puberty stage in HEALTHY was determined by self-assessment, which has been shown to be inaccurate, except to distinguish pre-puberty from puberty.¹⁸

Although others have shown low sensitivity and specificity for HbA1c to predict diagnosis of diabetes when compared with the “gold standard” OGTT in youth,^{4, 19, 20} we have previously demonstrated, using free-living continuous glucose monitoring, that the two tests, in fact, reflect different components of glycemia and are equally valid for identifying dysglycemia in youth who are obese.⁵ Thus, based on these data, the HbA1c remains a valid test when interpreted correctly. Because screening for dysglycemia increases when guidelines support the use of HbA1c as a screening test,²¹ we elected to focus on HbA1c in this analysis of the HEALTHY data.

Although the mean HbA1c was slightly higher in youth who were overweight or obese, the distribution of HbA1c in the overweight/obese cohort was very similar to the distribution in the normal weight cohort. Thus, a proportion of youth with obesity have a HbA1c in the adult “prediabetes” range, but these same HbA1c values are within the distribution for normal weight youth, raising questions about how meaningful the adult-based cutoffs are for defining prediabetes in youth. In fact, a previously published analysis of the HEALTHY cohort reported that, of those with a prediabetes HbA1c at baseline (6th grade, n=128), only 1 progressed to diabetes and 53 had a normal HbA1c at follow up (8th grade). Furthermore, of those who developed a diabetes range HbA1c in 8th grade, only 1 had an abnormal HbA1c at baseline.²² Furthermore, clinic-based follow-up in a pediatric population at high risk for diabetes suggests that risk for progression to diabetes is low with an HbA1c <6%.²³ Although large prospective longitudinal cohort studies exploring whether HbA1c, or any other measure of glycemia, can predict progression to diabetes in youth have not been done, these HEALTHY study results emphasize that the interpretation of prediabetes range HbA1c needs to be done with caution, even in youth with obesity.

The distribution curve in lean Non-Hispanic black youth in HEALTHY was shifted to the right compared with Hispanic and Non-Hispanic White youth. It is certainly possible that this is related to the relatively lower insulin sensitivity previously demonstrated in Black adolescents.^{24–26} However, a large study using intravenous tolerance testing to assess insulin sensitivity and secretion, has shown that Black youth adequately compensate for reduced insulin sensitivity during puberty and have no change in disposition index, which is the primary determinant of glycemia.²⁶ There are other potential explanations for the racial differences in HbA1c distribution, including common variants in the hemoglobin β -chain that can interfere with the HbA1c assay, even when using HPLC. In a large cohort of youth and adults with type 1 diabetes who had free-living glycemia measured by continuous glucose monitoring, Black participants had a higher HbA1c for the same average glucose than White participants.²⁷ Thus, the relationship between HbA1c and average glucose appears to be different between the two races.

This analysis was not designed to determine cut-points to best define prediabetes or to describe how best to predict risk for diabetes in youth. Rather, the goal was to take

advantage of the standardized measurement of HbA1c in this large cohort of otherwise healthy middle-school youth to explore the normal distribution of HbA1c in youth. We demonstrate here that this distribution extends into the adult-defined prediabetes range. It should be noted that the HEALTHY cohort is not necessarily representative of the national population, being disproportionately of minority race and ethnicity and with lower socioeconomic status, and we were unable to adequately control for pubertal status, both of which are limitations of this study. Furthermore, because >50% of both groups was of Hispanic ethnicity, results should be interpreted with caution in terms of generalizability to the U.S. population.

In summary, the HbA1c has become a useful tool to screen for diabetes and risk for diabetes due to wide availability, a high degree of standardization, and the convenience of being able to use this measurement in a non-fasted state. Indeed, the HbA1c is the most practical way to screen for diabetes. However, given that HbA1c values above the adult-defined ADA cutoff for prediabetes are seen in 2% of a large cohort of normal weight youth, and higher among non-Hispanic black youth, results in at-risk youth being screened for diabetes and prediabetes need to be interpreted with caution. Further studies are needed to better define the normal glycemic range in pubertal adolescents and to determine whether there is a pediatric HbA1c cut-point that optimally predicts progression to diabetes in at-risk youth.

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Figure: HbA1c distributions:

These histograms show the HbA1c frequency and distribution in the HEALTHY cohort, broken down by (a, b) weight status and (c-e) race/ethnicity. The vertical line denotes the cutoff for diagnosis of prediabetes by ADA criteria.

Table 1:

Normal weight participant demographics

	All	6 th Graders	8 th Graders
<i>Age (years, mean±SD)</i>	12.17 ± 1.26	11.36 ± 0.60	13.66 ± 0.64
<i>Sex, n (% Female)</i>	2526 (54.9)	1665 (55.6)	861 (53.4)
<i>Race/ethnicity, n (%)</i>			
<i>Hispanic</i>	2357 (51.2)	1511 (50.5)	846 (52.5)
<i>Black</i>	833 (18.1)	586 (19.6)	247 (15.3)
<i>White</i>	993 (21.6)	647 (21.6)	346 (21.5)
<i>Other</i>	420 (9.1)	248 (8.3)	172 (10.7)
<i>BMI z-score</i>	0.03 (0.73)	0.00 (0.73)	0.08 (0.71)
<i>BMI Percentile (mean ± SD)</i>	52.27 ± 23.58	51.24 ± 23.78	54.18 ± 23.09
<i>Self-report Tanner stage, n (%)</i>			
<i>Tanner 1</i>	323 (7.2)	316 (11.0)	7 (0.4)
<i>Tanner 2</i>	854 (19.1)	769 (26.8)	85 (5.3)
<i>Tanner 3</i>	1640 (36.7)	1201 (41.9)	439 (27.3)
<i>Tanner 4</i>	1525 (34.1)	552 (19.3)	973 (60.5)
<i>Tanner 5</i>	132 (3.0)	29 (1.0)	103 (6.4)
<i>HbA1c</i>	5.11 (0.29)	5.11 (0.29)	5.11 (0.30)
<i>Prevalence of abnormal HbA1c</i>			
<i>HbA1c <5.7%</i>	4504 (97.8)	2940 (98.3)	1564 (97.1)
<i>HbA1c 5.7% and <6.5%*</i>	99 (2.2)	52 (1.7)	47 (2.9)